Gemfibrozil Treatment Increases Low-density Lipoprotein Particle Size in Type 2 Diabetes Mellitus but Does Not Alter *in vitro* Oxidizability

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The aim of this study was to determine the effect of the lipid modifying agent gemfibrozil on lipid and coagulation risk factors in patients with Type 2 diabetes mellitus (Type 2 DM). Twenty-six subjects with Type 2 DM and dyslipidaemia were treated for 24 weeks with either gemfibrozil 600 mg orally twice daily or placebo in a double-blind randomized trial. Lipid profiles, fibrinogen, Factor VII, and plasminogen activator inhibitor-1 (PAI-1) were measured by routine laboratory methods. Low density lipoprotein (LDL) size was determined by gradient gel electrophoresis and the resistance of LDL to copper-induced oxidation was assessed by measuring absorbance at 234 nm. Gemfibrozil significantly reduced total cholesterol (–0.9 (–0.48, –1.32) mmol l^{-1}; $p < 0.05$) and triglycerides (–2.7 (–1.55, –1.35) mmol l^{-1}; $p < 0.001$) vs placebo. The fall in triglyceride was reflected by a fall in VLDL cholesterol levels in the gemfibrozil treated group vs placebo (–1.31 mmol l^{-1}; $p < 0.001$). LDL-cholesterol level did not change but LDL particle size increased by 0.5 nm (0.01, 0.93); $P < 0.02$. The increase in particle size was inversely correlated with the change of triglyceride level ($r = -0.79$, $p < 0.0001$) but did not result in any reduction of susceptibility to copper-induced oxidation. There were no significant changes in the coagulation parameters studied. Because of its ability to correct the lipid abnormalities associated with Type 2 DM particularly hypertriglyceridaemia, gemfibrozil provides a useful therapeutic option in the management of diabetic dyslipidaemia but it does not alter *in vitro* oxidizability of LDL. © 1998 John Wiley & Sons, Ltd.

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Introduction

Type 2 diabetes mellitus (Type 2 DM) is a metabolic disorder of which hyperglycaemia is the hallmark but which is also characterized by abnormalities of lipid metabolism.[1–4] In particular, elevated levels of triglycerides and reduced levels of high density lipoprotein (HDL) cholesterol have been well described[5–8] and are thought to contribute significantly to the greatly increased risk of cardiovascular disease in these patients.[9–14] Recently, another lipid risk factor for atherosclerotic cardiovascular disease has been identified, namely small low density lipoprotein (LDL) particle size.[15,16] A predominance of small LDL particles is found more frequently in patients with Type 2 DM and has been linked with other abnormalities of diabetic dyslipidaemia, such as hypertriglyceridaemia and reduced HDL-cholesterol level.[17–19] This dyslipidaemic profile may play an important role in the development of atherosclerosis in Type 2 DM and has recently been related to the presence of endothelial dysfunction in this group of patients.[20]

Oxidation of LDL is considered to be an important step in the development of atherosclerosis. *In vivo*, this is believed to occur within the subintimal space and involves modification by free radicals of the polyunsaturated fatty acids in LDL.[21,22] Peroxide groups subsequently attach to the lysine groups on apoprotein B, decreasing its affinity for the LDL receptor.[23] In addition, the oxidized LDL has an increased affinity for the scavenger receptor on macrophages, which is not susceptible to down-regulation and may contribute to the formation of foam cells.[24] Oxidized LDL may also be directly toxic to

Abbreviations: CETP cholesterol ester transfer protein; HDL high density lipoprotein; LDL low density lipoprotein; PAI-I plasminogen activator inhibitor-1; PPAR peroxisone proliferator activated receptor; VLDL very low density lipoprotein

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endothelial cells.[25] Previous studies indicate that small LDL particles may be more susceptible to oxidation by free radicals and therefore are thought to be potentially more atherogenic.[21,22]

Treatment of lipid abnormalities in patients with Type 2 DM has been widely recommended, even though the benefit in terms of clinical outcome has not been tested extensively in this population. Arguably, fibric acid derivatives are the most suitable choice for the treatment of diabetic dyslipidaemia, as they reduce triglycerides and increase HDL-cholesterol levels[26–33] and so ameliorate the major abnormalities of this condition. Nicotinic acid can also achieve these goals, but it is less well tolerated and worsens hyperglycaemia,[34] probably by increasing insulin resistance.[35]

Gemfibrozil is a widely used fibric acid derivative whose efficacy in the treatment of diabetic dyslipidaemia has been well established.[26–33] However, few studies have extended for as long as 6 months and or have addressed the effects of gemfibrozil on LDL particle size in diabetes.[33] The study reported here was undertaken to examine the lipid response to 24 weeks' gemfibrozil treatment in patients with diabetic dyslipidaemia and in particular to determine the effect of treatment on LDL particle size and susceptibility to oxidation.

Patients and Methods

Patients

Twenty-six patients with Type 2 DM[36] were recruited for the study from St Vincent's Hospital (SVH), Monash Medical Centre (MMC), and The Geelong Hospital, Victoria, Australia. For entry into the study, the combination of total cholesterol level >5.5 mmol l^{-1}, total triglyceride level >2.3 mmol l^{-1}, and an HDL-cholesterol level >1.1 mmol l^{-1} were required. Subjects with total cholesterol or total triglyceride levels >8.0 mmol l^{-1} were excluded. Patients were clinically stable and had not been on lipid modifying medication for at least 2 years. None was macroproteinuric or on antioxidant vitamin supplements. Patient characteristics are summarized in Table 1.

Clinical Protocol

The study was approved by the Human Research Ethics Committees at each hospital and all subjects gave written, informed consent to participate in the study. Subjects were randomized in double-blind fashion to either active treatment with gemfibrozil 600 mg orally twice daily or placebo. Both groups were given appropriate dietary advice. Exercise levels were held constant throughout the study period.

The subjects attended an initial screening visit and returned for baseline, 6, 12, 18, and 24 week visits, at which times blood was collected following a 12 h overnight fast. Samples were taken for determination of lipid profile including lipoprotein and apolipoprotein measurements, at each visit; fasting glucose was measured at baseline, 6 and 24 weeks; HbA_{1c}, fibronogen, Factor VII, and plasminogen activator inhibitor-1 (PAI-1) levels were measured at baseline, 12 and 24 weeks. Samples for determination of LDL particle size and susceptibility to oxidation were collected at baseline and 24 weeks on a subset of subjects from two of the centres involved in the study (SVH and MMC).

Laboratory Methods

For lipid and lipoprotein analyses 10 ml of blood was collected in an EDTA-containing tube from all subjects. Plasma was separated by centrifugation at 1300G for 15 min at 4 °C. Total plasma cholesterol (cholesterol oxidase, Trace Scientific, Melbourne, Australia), total plasma triglycerides (glycerol-3-phosphate oxidase, Trace Scientific, Melbourne, Australia) were performed as part of a routine automated laboratory enzymatic assay on an Olympus AU5031. The coefficient of variation (CV) for cholesterol was 1.6 % and 0.9 % at 3.2 mmol l^{-1} and 7.8 mmol l^{-1}, respectively. For triglycerides the CV was 1.9 % at 1.0 mmol l^{-1} and 1.8 % at 2.2 mmol l^{-1}. HDL-cholesterol was assayed following polyethylene glycol 6000 precipitation of non-HDL lipoproteins. CV was 5.5 % at 2.03 mmol l^{-1} and 4.0 % at 0.97 mmol l^{-1}. LDL-cholesterol was calculated using the Friedewald equation[37] if the total triglyceride level was ≤ 4.5 mmol l^{-1}. For higher levels, very low density lipoprotein (VLDL) was isolated by ultracentrifugation and cholesterol measured separately. In these cases, LDL cholesterol was calculated by subtraction of HDL- and VLDL-cholesterol levels from the total cholesterol level. Assay of apolipoprotein(a) (apo(a)) levels was performed by immunoradiometric assay using a commercial kit (Pharmacia, Uppsala, Sweden). Interassay CV was 14 % at 112 U l^{-1} and 9 % at 380 U l^{-1}. Apolipoprotein A1 (apo A1) and apolipoprotein B (apo B) were measured by immunonephelometry using a commercially available kit (Kallestad Diagnostics Inc., Chaska, MN, USA). CV for apo A1 was 0.7 % at 2.47 g l^{-1} and 3.0 % at 0.77 g l^{-1}. CV for apo B was 6.2 % at 1.38 g l^{-1} and 3.1% at 0.4 g l^{-1}. HbA_{1c} was assayed on blood collected in EDTA by ion exchange high performance liquid chromatography with the inter-assay coefficient of variation (CV) of 5 %.

Blood collected in EDTA was also used for LDL particle size determination. Plasma was separated and LDL isolated by adjusting the density of 4 ml of plasma to 1.21 g ml^{-1} by the addition of 1.31 g of KBr. This plasma was then pipetted into an ultracentrifuge tube and overlayered with a 1.006 g ml^{-1} NaCl solution. The tubes were sealed and placed in a Beckman (Palo Alto, CA) VTi65.1 rotor and spun at 65 000 rev min^{-1} for 90 min at 7 °C with acceleration and deceleration parameters set at 5. Following ultracentrifugation the LDL formed a visible band in the centre. The ultracentrifuge tube was punctured and the LDL aspirated.[38] LDL particle diameter

Table 1. Clinical characteristics of Type 2 DM subjects with dyslipidaemia treated for 24 weeks with gemfibrozil or placebo

	Active		Placebo	
	Baseline	Post-treatment	Baseline	Post-treatment
(Male/female)	8/6		9/3	
Age (yr)	58 ± 7		57 ± 6	
BMI (kg m^{-2})	33 ± 8	33 ± 8	31 ± 6	29 ± 6
Diet treatment alone (%)	14	14	8	8
Oral hypoglycaemics (%)	72	72	67	67
Insulin (%)	14	14	25	25
β-blocker (%)	7	7	17	17
Diuretic (%)	35	35	17	17
Fasting glucose (mmol l^{-1})	9.9 ± 4.9	10.2 ± 4.1	11.7 ± 6.9	11.2 ± 4.5
HbA_{1c} (%)	7.5 ± 2.2	8.0 ± 2.2	7.8 ± 1.4	7.7 ± 1.4

All results are expressed as mean ± SD.

was determined as previously described[39,40] using commercially available 3–13 % non-denaturing native gels (Gradipore Ltd, Sydney, Australia). The gels were scanned to determine the distance of the LDL peak from the origin. Particle diameter was calculated using a regression equation derived from the position of standards of known diameter by plotting the log of the standards against their positions on the scanned gel. A statistical package was used to plot a regression and derive a formula allowing unknown samples to be sized. CV on a 26.1 nm quality control sample run on every gel was 0.8 %.

For measurement of oxidation parameters, 10 ml of blood was collected in lithium heparin from a subset of 16 subjects recruited from two of the participating centres (MMC and SVH) and plasma was separated. LDL was first isolated by vertical density ultracentrifugation as described above and further purified by a Sephadex G-25 column at 4 °C in the dark. Copper initiated lag time was determined by a modification of the method described by Esterbauer;[41] 5 μmol copper was added to isolated LDL diluted to 150 μmol l^{-1} cholesterol in phosphate buffered saline. The generation of products resulting from the oxidation of lipids was followed by measuring absorbance at 234 nm. The lag time was calculated as the intercept between the initial velocity and the maximum velocity. The peak height was calculated as the difference between the initial absorbance and the maximum absorbance and is given in absorbance units. The maximum velocity is given in Δ absorbance min^{-1}. The lag time is considered a measurement of the resistance of the LDL particle to damage by free radicals leading to oxidation, and the peak height a measure of the degree of oxidation achieved. All lag time determinations were performed within 3 h of the blood being drawn. The CV on repeated determinations of lag time on LDL obtained from a control subject, who was on a stable diet, was 15 %.

For coagulation studies, blood was collected into 5 ml tubes containing tri-sodium citrate (0.109 mol l^{-1}) and placed on ice. The plasma was separated and assayed within 24 h for fibronogen. All aliquots for Factor VII and PAI-1 assays were frozen at –70 °C and later thawed at 37 °C for 10 min prior to assay. The fibrinogen concentration of the plasma samples was determined on the Automated Coagulation Laboratory (ACL-Instruments Laboratories, Milan, Italy) by measuring the change in optical density at 660 nm before and after clotting. The optical density value of the samples was converted to a fibrinogen value from a concentration curve of stored standards (Behring Diagnostics, Marburg, Germany) to derive the fibrinogen value. Plasma samples with fibrinogen concentrations of greater than 8.0 g l^{-1} were diluted 1 in 2 with barbitone buffered saline, pH 7.3 and re-assayed. The inter-assay CV for fibrinogen was 5.9 %.[42] Factor VII levels were determined on samples diluted 1 in 10 and 1 in 20 with barbitone buffered saline, pH 7.3. Calibration and control samples (Behring Diagnostics, Marburg, Germany) were included in each assay run. The plasma samples were analysed on the ACL instrument, which constructs a new assay curve on each run and the results were derived from the standard curve. The inter-assay CV for Factor VII was 3.3 %.[43] PAI-1 levels were measured by ELISA,[44] using a commercially available kit (American Diagnostica Inc., Greenwich, CT, USA). Absorbance was measured at 492 nm. Samples containing greater than 50 ng ml^{-1} were diluted and reassayed. The inter-assay CV for PAI-1 was 5.3 %.

Statistical Methods

Statistical analysis was aimed at testing the hypothesis of equivalent change in lipid parameters between patients treated with gemfibrozil and placebo. As the study was designed as a repeated measure experiment, the main statistical model used was the repeated analysis of variance (ANOVA) model.[45] In this model, the effect of differences between patients, between treatment groups, between visits and the interaction effects between treatment groups and visits were considered. The test for the effect of treatment was constructed as the F ratio of

mean squares attributed to between treatment groups over the mean squares attributed to between patients. Ninety-five per cent confidence intervals of differences between groups were constructed based upon standard errors derived from the ANOVA model. The analysis variable in this model was the change from baseline, expressed both as absolute change and per cent change. The analysis was performed for each parameter separately. In addition, baseline differences between treatment groups in lipid parameters and demographic characteristics were tested using the unpaired *t*-statistic and the likelihood ratio chi-square statistic whenever appropriate. All computation and data analyses were performed using the SAS statistical analysis system (SAS Institute Inc., Cary, NC, USA).

Results

Gemfibrozil treatment did not influence body mass index (BMI), fasting glucose concentration or HbA_{1c} level (Table 1).

Changes in the lipid parameters, expressed as absolute change, are summarized in Table 2. Results obtained from analysis of the data based upon absolute change and percentage change were identical, so only absolute differences in the changes observed between gemfibrozil and placebo study groups with 95 % confidence intervals are described below. The changes observed at 24 weeks were apparent at 6 weeks and did not alter significantly over the time course of the study. A significant decrease was noted in total cholesterol levels when the study subjects on gemfibrozil were compared to those on placebo (–0.9 [–0.48, –1.32] mmol l^{-1}; $p < 0.05$). This difference between the two study groups resulted from changes in VLDL cholesterol (–1.31 [–0.71, –1.91] mmol l^{-1}; $p < 0.001$), with no significant differences in LDL cholesterol. No differences were noted between changes of total Apo B in the gemfibrozil and placebo treatment groups. A significant decrease in total triglyceride levels was noted, when subjects on gemfibrozil were compared to those on placebo (–2.7 [–1.55, –3.85] mmol l^{-1}; $p < 0.001$). The increase in HDL cholesterol level in those on gemfibrozil, when compared to those on placebo, failed to achieve statistical significance though a trend was observed (0.07 [–0.17, 0.31] mmol l^{-1}; $p = 0.08$). No significant change in apo(a) level was observed in those on gemfibrozil.

Data regarding LDL particle size and oxidation are shown in Table 3. A significant increase in LDL particle diameter was observed in the subjects on gemfibrozil, when compared to the placebo group (0.5 [0.01, 0.93] nm; $p < 0.02$). Changes in LDL particle size and triglyceride level corresponded significantly (Figure 1). No change in the resistance of LDL to oxidation or total oxidizability was observed.

Table 4 provides a summary of the results from the analysis of coagulation factors. None of the changes achieved statistical significance, although a trend was observed with those subjects on gemfibrozil, for an increase in fibrinogen levels when compared to those on placebo (0.9 [–0.17, 1.97] g l^{-1}; $p = 0.08$).

Table 2. Concentrations of plasma lipids, lipoproteins, and apolipoproteins in Type 2 DM treated for 24 weeks with gemfibrozil or placebo

Parameter	Baseline		Absolute change between week 24 and baseline			*p*
	Gemfibrozil	Placebo	Gemfibrozil	Placebo	Gemfibrozil–Placebo[a]	
Total cholesterol (mmol l^{-1})	6.2 ±0.58	6.1 ±0.47	–0.2 ±0.52	0.7 ±0.45	–0.9 (–0.48, –1.32)	<0.05
HDL cholesterol (mmol l^{-1})	0.85 ±0.106	0.88 ±0.122	0.12 ±0.3	0.05 ±0.24	0.07 (–0.17, 0.31)	NS
LDL cholesterol (mmol l^{-1})	3.8 ±0.53	3.5 ±0.81	0.5 ±0.71	0.4 ±0.62	0.1 (–0.51, 0.71)	NS
Total triglycerides (mmol l^{-1})	3.5 ±1.36	4.4 ±1.83	–1.5 ±1.42	1.2 ±1.25	–2.7 (–1.55, –3.85)	<0.001
VLDL cholesterol (mmol l^{-1})	1.61 ±0.58	1.50 ±0.71	–0.86 ±0.97	0.45 ±0.55	–1.31 (–0.71, –1.91)	<0.001
Apo B (ng dl^{-1})	133 ±11	140 ±11	–2 ±14	21 ±12	–23 (–14, –31)	NS
Apo A-1 (ng dl^{-1})	117 ±18	127 ±24	2 ±7	8 ±6	–6 (–1, –11)	NS
Log Apo (a) IU l^{-1}	4.58 ±1.97	4.92 ±1.72	3.21 0.48	1.10 ±0.75	2.11 (0.96, 3.26)	NS

Values are mean ± SD of changes between week 24 and baseline, calculated from the repeated analysis of variance model.
[a]Ninety-five per cent confidence interval was calculated for difference between Gemfibrozil and placebo group.

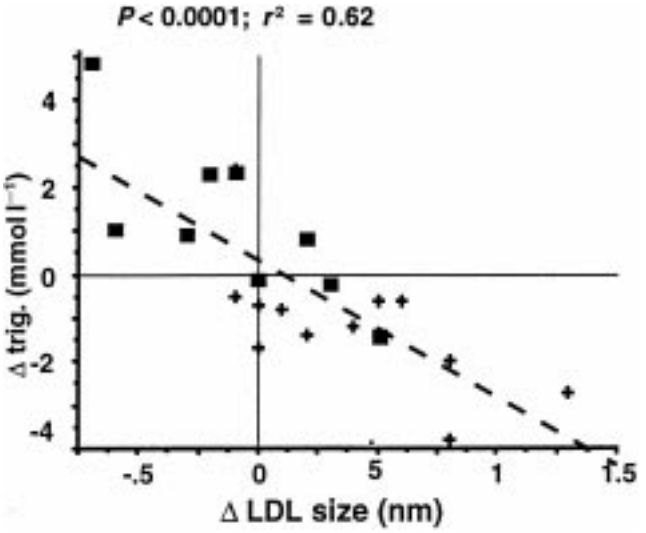

Figure 1. Plot of the changes in triglyceride levels (Δ trig.) vs the change in low density lipoprotein particle size (Δ LDL size) after treatment of Type 2 DM subjects with dyslipidaemia; + gemfibrozil, ■ placebo

Discussion

The most significant change in the lipid profile as a result of gemfibrozil therapy over 6 months was the 40 % reduction of triglycerides, mirrored by a 50 % reduction of VLDL-cholesterol, changes similar to those reported previously.[26–33,46] Gemfibrozil has multiple effects on lipid metabolism, acting in part through the nuclear receptor peroxisome proliferator-activated receptor (PPAR).[47] Two of the key actions of gemfibrozil that result in the lowering of triglyceride concentration are activation of lipoprotein lipase[48] and reduction of hepatic VLDL output.[49] The change in triglycerides was accompanied by an increase in HDL-cholesterol, again comparable to that found in earlier studies, though this did not reach statistical significance. The full effect of gemfibrozil on the lipid profile was seen by 6 weeks and both triglyceride and HDL-cholesterol were then maintained until the end of the study at 24 weeks.

Compared with placebo, gemfibrozil appeared in this study to be neutral in its effect on LDL-cholesterol levels. In previous studies of patients with Type 2 DM the effect of gemfibrozil on LDL-cholesterol has varied, depending on the initial triglyceride level. When triglycerides are normal, LDL-cholesterol tends to fall,[28] but when triglycerides are very high, LDL-cholesterol levels rise with gemfibrozil treatment.[26] Although the level of LDL-cholesterol did not change in this study, there was a significant increase in LDL particle size with gemfibrozil treatment. These findings are consistent with a previous study.[33] It is clear that this action of gemfibrozil is directly related to its effect on triglycerides, as there was a close correlation between the fall in triglycerides and the increase in LDL particle size. This inverse relationship between triglyceride level and LDL particle size may be mediated by cholesteryl ester transfer protein (CETP), which exchanges triglyceride in VLDL for cholesterol in HDL resulting in triglyceride-rich HDL, which is then hydrolysed.[50] As small, dense LDL particles are cholesterol depleted and triglyceride enriched[51] they may arise via a similar mechanism, although this possibility remains to be demonstrated.

There was no effect of gemfibrozil treatment on glycaemic control in this study. Improvement in glucose

Table 3. Effect of treatment with gemfibrozil or placebo on LDL particle size and lag time

Parameter		Baseline		Absolute change between week 24 and baseline			*p*
		Gemfibrozil	Placebo	Gemfibrozil	Placebo	Gemfibrozil–Placebo[a]	
LDL diam (nm)	Gemfibrozil (*n* = 11)	24.9	24.9	0.4	–0.1	0.5	<0.02
	Placebo (*n* = 9)	±0.5	±0.4	±0.4	±0.5	(0.01, 0.93)	
Lag time (min)	Gemfibrozil (*n* = 9)	61 ±21	65 ±15	–1 ±13	–4 ±27	3 (–13, 19)	NS
	Placebo (*n* = 7)						
Max vel (ΔA[b] min)	Gemfibrozil (*n* = 9)	0.019 ±0.004	0.018 ±0.004	0.002 ±0.008	–0.001 ±0.004	0.003 (–0.002, 0.009)	NS
	Placebo (*n* = 7)						
Peak height (A)[b]	Gemfibrozil (*n* = 9)	0.74 ±0.17	0.62 ±0.07	0.01 ±0.07	0.03 ±0.02	–0.02 (–0.15, 0.20)	NS
	Placebo (*n* = 7)						

Values are mean ± SD of changes between week 24 and baseline, calculated from the repeated analysis of variance model.
[a]Ninety-five per cent confidence interval was calculated for difference between gemfibrozil and placebo group.
[b]A, absorbance measured at 234 nm in arbitrary units.

Table 4. Effect of treatment with gemfibrozil or placebo on fibrinogen, Factor VII, and PAI-1 levels

Parameter	Baseline		Absolute change baseline–week 24 and baseline			*p*
	Gemfibrozil	Placebo	Gemfibrozil	Placebo	Gemfibrozil–Placebo[a]	
Fibrinogen ($g\ l^{-1}$)	4.0 ±0.58	3.9 ±0.92	0.8 ±1.17	–0.1 ±0.55	0.9 (–0.17, 1.97)	NS
Factor VII ($IU\ l^{-1}$)	1.25 ±0.40	1.00 ±0.53	0.1 ±0.58	–0.05 ±0.49	0.15 (–0.35, 0.65)	NS
Log PAI-1 ($ng\ ml^{-1}$)	4.01 ±0.75	3.49 ±0.57	–0.02 ±0.60	0.14 ±1.17	–0.16 (–1.11, 0.80)	NS

Values are mean ± SD of changes between week 24 and baseline, calculated from the repeated analysis of variance model.
[a]Ninety-five per cent confidence interval was calculated for difference between gemfibrozil and placebo group.

tolerance and reduction of the insulin response after an oral glucose load have been reported with gemfibrozil treatment, particularly in patients with less satisfactory initial glycaemic control.[52] However, most previous studies have reported a neutral effect on fasting glucose concentrations[53,54] and insulin action on glucose and non-esterified fatty acid metabolism.[55]

Elevated triglycerides and low HDL-cholesterol are the predominant lipid abnormalities found in Type 2 DM patients and are important risk factors for coronary heart disease.[9–14] The reduced LDL particle size of Type 2 DM[17–19] represents an important part of the lipid risk factor profile. Small, triglyceride-rich LDL particles may be particularly atherogenic because they are more prone to oxidation.[21,22] We had hypothesized that an increase in LDL particle diameter with gemfibrozil treatment might reduce susceptibility to oxidation. The increase in LDL particle size without change of LDL resistance to copper-induced oxidation is consistent with the findings of Bredie *et al.*,[56] who studied a non-diabetic cohort. The compositional changes accompanying the increase in LDL particle size following treatment with gemfibrozil may have been insufficient to cause a detectable change in resistance to copper-induced oxidation or in the degree of oxidation achieved. It is possible that a longer or larger study may have detected an effect.

As has been reported previously in a non-diabetic population, we found a tendency for fibrinogen level to rise in the treatment group.[57] Bezafibrate may offer theoretical advantages over gemfibrozil as it has been shown to decrease fibrinogen and PAI-1.[58] Both PAI-1 and Factor VII levels have been reported to be elevated in association with hypertriglyceridaemia[59,60] and so we measured levels before and after reduction of triglycerides with gemfibrozil. There was no change in levels with treatment, but there is considerable biological variation in these parameters and a larger study group may be required to demonstrate any change linked with the reduction of triglycerides.

The effects of gemfibrozil on the dyslipidaemia of diabetes should make it a suitable choice for treatment of this condition, which is associated with such greatly increased risk of cardiovascular disease. However, the final evidence for benefit from treatment would be the demonstration of a reduction of cardiovascular events in a treated population of diabetic patients. In the Helsinki Heart Study, it is perhaps relevant that the greatest benefit from treatment was seen in men with combined abnormalities of the lipid profile.[46] Unfortunately, too few diabetic patients were included to produce a significant result in this subgroup, even though the coronary heart disease incidence in the treated patients was only a third that of the control group.[61] Demonstration of clinical benefit from treatment of diabetic dyslipidaemia with gemfibrozil or other fibric acid derivatives will require intervention studies specifically designed for the diabetic population.

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